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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/669,976	09/24/2003	Holger Engel	QGN-038.1 US	8390
29425	7590	10/28/2008	EXAMINER	
LEON R. YANKWICH 201 BROADWAY CAMBRIDGE, MA 02139			MUMMERT, STEPHANIE KANE	
			ART UNIT	PAPER NUMBER
			1637	
			MAIL DATE	DELIVERY MODE
			10/28/2008	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Advisory Action  
Before the Filing of an Appeal Brief**

<b>Application No.</b> 10/669,976	<b>Applicant(s)</b> ENGEL ET AL.
<b>Examiner</b> STEPHANIE K. MUMMERT	<b>Art Unit</b> 1637

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 01 October 2008 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☐ The period for reply expires \_\_\_\_\_ months from the mailing date of the final rejection.  
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.  
Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**NOTICE OF APPEAL**

2. ☒ The Notice of Appeal was filed on 01 October 2008. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

**AMENDMENTS**

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because  
(a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);  
(b) ☐ They raise the issue of new matter (see NOTE below);  
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or  
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.  
NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).  
5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.  
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).  
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.  
The status of the claim(s) is (or will be) as follows:  
Claim(s) allowed: \_\_\_\_\_.  
Claim(s) objected to: \_\_\_\_\_.  
Claim(s) rejected: 1, 2, 4-16 and 23-25.  
Claim(s) withdrawn from consideration: 17-22.

**AFFIDAVIT OR OTHER EVIDENCE**

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).  
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).  
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

**REQUEST FOR RECONSIDERATION/OTHER**

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.  
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). \_\_\_\_\_.  
13. ☐ Other: \_\_\_\_\_.

/GARY BENZION/  
Supervisory Patent Examiner, Art Unit 1637

/Stephanie K. Mummert/  
Examiner, Art Unit 1637

Continuation of 11, does NOT place the application in condition for allowance because: Applicant argues that the instant invention rests on the surprising discovery that "in a multiplex PCR reaction, the inclusion of a chemically-modified hot start DNA polymerase together with a volume exclusion agent in a standard PCR reaction with equimolar concentrations of all primers (thereby eliminating a labor-intensive step from the set up of the reaction) led to good yields of all amplified targets" (p. 3 of remarks). Applicant also points to portions of the specification and the figures to illustrate Applicant's invention.

This summary is noted and is appreciated as it does serve to focus the future discussion of the merits of the application. However, these portions of the specification and the accompanying arguments are not persuasive, for reasons that will be discussed in more detail below.

Regarding the art rejections, Applicant traverses the rejection and applies an extremely narrow scope of the individual reference. For example, regarding Backus, Applicant states "the Backus reference does not teach the combination of a volume exclusion agent and a chemically-modified hotstart DNA polymerase for the coamplification of two or more target nucleic acids" and that "Backus teaches that, although volume exclusion agents are known to increase hybridization rates, they should only be used in PCR in a very limited set of circumstances". Applicant also asserts that "Backus only allows that the use of a volume exclusion agent in combination with an antibody-inactivated polymerase may be suitable under very limited hybridization conditions" and points to the examples which exemplify the coamplification of a low copy number target with a high copy number target.

However, Applicant is arguing a misreading of the teaching of Backus. First, it is noted that the portion of the specification in column 2 where the statements are made regarding "use not recommended" are not the teachings of Backus, they reference the position of Sambrook specifically. Further, this passage is referenced again at col. 4, lines 47-55, where it is noted that "in view of the teaching of the art, notably, Sambrook et al., one would not use volume exclusion agents in amplification methods" and concludes "This does not appear to be the case with the present invention. The advantages provided by the present invention, then, were not expected." Therefore, Applicant is mischaracterizing Backus for at least this passage.

The assertion that Backus "does not teach the combination of volume exclusion agent and a chemically-modified hot start DNA polymerase for the coamplification of two or more target nucleic acids" is also incorrect. While Backus may exemplify the preferential amplification of one target over another, the disclosure clearly includes coamplification of one or more nucleic acids. Col. 2-4, discuss the "coamplification of two or more target nucleic acids" repeatedly, see col. 2, line 67; col. 3, lines 22-24. It is also noted, the claims do not require a step directed to the detection of products which are represented equally, as argued in the response.

Applicant goes on to address Bustin and characterizes it as a review and concludes "Bustin relates to normalization of an RT-PCR reaction using an RNA with known in vivo expression levels" (p. 8 of remarks).

It is agreed that Bustin teaches normalization, however, despite Applicant's interpretation, Bustin does teach the coamplification of two target sequences that are present at similar copy numbers, as required by the instant claims. Therefore, in view of the teaching of Bustin, it would have been obvious to apply the method of Backus in additional settings, including where the target sequences are present at similar copy number.

Finally, Applicant addresses Birch and notes that they "do not teach or suggest the use of a hotstart enzyme in combination with a volume exclusion agent for use in a multiplex PCR reaction".

As noted above, Birch does not stand alone and is relied upon for the modification of a thermostable enzyme with dicarboxylic acid anhydride and is not relied upon for multiplex PCR or for amplification in the presence of a volume exclusion agent.

For these reasons, the arguments are not persuasive and the rejection has been maintained.

The arguments for the remaining dependent claims rely upon the arguments applied for Backus, Bustin and Birch. These arguments are not persuasive for the reasons stated above.